Can We Replace Opinion Consensus with a Bayesian Process?

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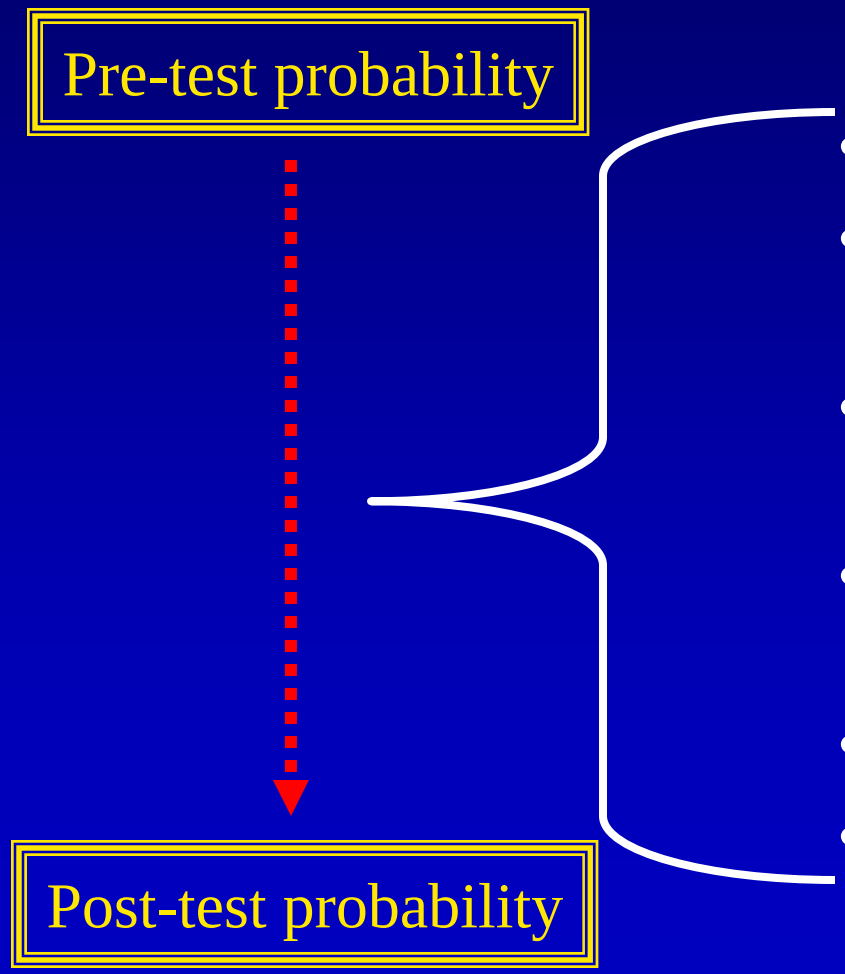
Causality Assessment

- Accurate assessment of causality with DILI is very challenging but essential
- Current instruments for causality assessment (e.g., RUCAM/CIOMS) are inadequate
- Given the resources and expertise of the DILIN, we have a unique opportunity to improve the causality assessment of DILI

Causality Assessment



- Is the “signature” correct?
- Have competing causes been excluded?
- Are drug-specific risk factors present?
- Is timing (latency, dechallenge) consistent?
- Is rechallenge positive?
- Is histology consistent (if available)?

RUCAM

Positive

- Easy to use
- Reproducible (+/-)
- Valid (?)

Negative

- Seemingly arbitrary scoring
- Inflexible/simplistic
- Valid ?
- Does not deal well with missing data

What we have…

DILIN

Drug-Induced Liver Injury Network

What we want…

Expert Opinion

Positive

- Available (DILIN)
- Flexible
- Probably more accurate than RUCAM

Negative

- Not reproducible
- Component parts of opinion are not stated or quantified
  - Problem wrt publication
- Requires experts
- Valid?

A Bayesian Approach

Positive

- Takes into account prior probability of DILI
- Drug-specific risk factors and “signatures”
- Deals well with missing data
- Flexible
- Novel

Negative

- Labor intensive to develop*
- Necessary data may be difficult to find or not be available
- Valid?
- Not as easy to use as RUCAM

**But hopefully easy to use*

A Bayesian Approach

- Prior probability - based on literature
- “Signature”, drug-specific risk factors - taken into consideration in determining the post-test probability
- Post-test probability is numerical
    - No fuzzy terms - “possible”, “probable”…
- Big advantage vs. RUCAM-type scales wrt dealing with missing data

A Bayesian Approach

- Initial probability estimate of DILI is modified by additional case-specific information
- Prior odds (PrO) = expected drug-attributable risk of abn LFTs / background risk of abn LFTs
- Likelihood ratio (LR) - information of differential diagnostic value
- Posterior odds = PrO x LR1 x LR2 x LR3 x LR4…

Three Steps

1. Determine the initial/prior probability of DILI
2. Incorporate additional case-specific information
3. Determine final DILI probability for that case

- Courtesy of J. Rochon

Prior Probability

- Establish a database of drug-specific prior probabilities based on:
  - RCTs - published and unpublished
  - Case studies - published and unpublished
  - Standard texts
  - Expert opinion
  - Etc.

Prior Probability

- Since DILI is rare, poorly understood, idiosyncratic, and contextual ---> creation of such a database would be challenging
  - U.S. National Library of MedicineHepatotoxicity Web of Knowledge (Jack Synder)
- Probability of mild injury vs. severe injury?
- Could drugs be grouped by pattern of liver injury usually observed?

Case Specific Information
Likelihood Ratios

- LR - the likelihood that a given test result would be expected in a patient with the target disorder compared with the likelihood that that same result would be expected in a patient without the target disorder
  - LR+ = probability of an individual w/ condition having a + test / probability of an individual w/out the condition having a positive test
  - LR- = probability of an individual w/ condition having a - test / probability of an individual w/out the condition having a negative test

Likelihood Ratios

- Less influenced by changes in prevalence compared with sensitivity and specificity
- Can be calculated for several levels of a test/symptom/sign
- Can be used to combine the results of multiple tests

Likelihood Ratios

- If no information: LR = 1 and pretest = post-test probability
- Ideally based on data from RCT
  - "conservative estimates based on clinical experience and consensus among us"

Harry A. Guess

(December 24, 1940 - January 1, 2006)

"To make the process worthwhile, these component LRs should be estimated using data to the maximum extent possible and falling back on expert opinion only when data are not available."

Likelihood Ratios

- LR+ = sensitivity / (1-specificity)
  = TPR / FPR
- LR- = (1 - sensitivity) / specificity
  = FNR / TNR
- If LR > 1: post-test prob > pretest prob
  - LR > 10 usually clinches dx
- If LR < 1: post-test prob < pretest prob
  - LR < 0.1 usually rules out dx

Likelihood Ratios

- Some examples:
  - AP (for liver mets) LR+ 3.8 LR- 0.31
  - ANA (for SLE) LR+ 4.5 LR- 0.13
  - EKG (for MI) LR+ 30 LR- 0.44
  - US (for stones) LR+ 18 LR- 0.15
  - EGD (ulcer) LR+ 100 LR- 0.05

Likelihood Ratios

- Potential LRs of interest:
  - LR_{Age}, LR_{Gender}, LR_{Race}
  - LR_{ALT}, LR_{AP}, LR_{Tbili}
  - $LR_{competing\ causes}$
  - $LR_{Latency}$
  - $LR_{Dechallenge}$
  - LR_{Rash}
  - LR_{Etc}

Diagnostic Test Parameters

2 x 2 Table

Patient Status ("Truth")

Test Result	Disease Present	Disease Absent	Total # of patients
Positive	True positive (A)	False positive (B)	With positive test (A + B)
Negative	False negative (C)	True negative (D)	With negative test (C + D)
Total # of patients	With disorder (A + C)	Without disorder (B + D)	(A + B + C + D)

PPV = A / A + B

NPV = D / C + D

Sens = A / A + C

Spec = D / B + D

Accuracy = A + D / A + B + C + D

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Negative	False negative (C)	True negative (D)	With negative test (C + D)
Total # of patients	With disorder (A + C)	Without disorder (B + D)	(A +B + C + D)

Sens = A / A + C

Spec = D / B + D

LR+ = (A / A + C) / (B / B + C)

LR- = (C / A + C) / (D / B + D)

Determining Final DILI Probability

- Pre-test odds = prevalence / (1- prevalence)
  - Prevalence = (A + C) / (A + B + C + D)
- Post-test odds = pre-test odds x LR
- Post-test probability = pre-test odds / (post-test odds / (post-test odds + 1)

A Bayesian Approach

- Computer-based (Web or Palm)
  - BRCAPRO - Duke Institute for Statistics and Decision Sciences
- Requires utilizing or (more likely) establishing a sophisticated database
  - Top 100 most toxic drugs?
  - Drugs dealt with as categories rather than individual agents
  - Feasible? Overly ambitious?

A Bayesian Approach

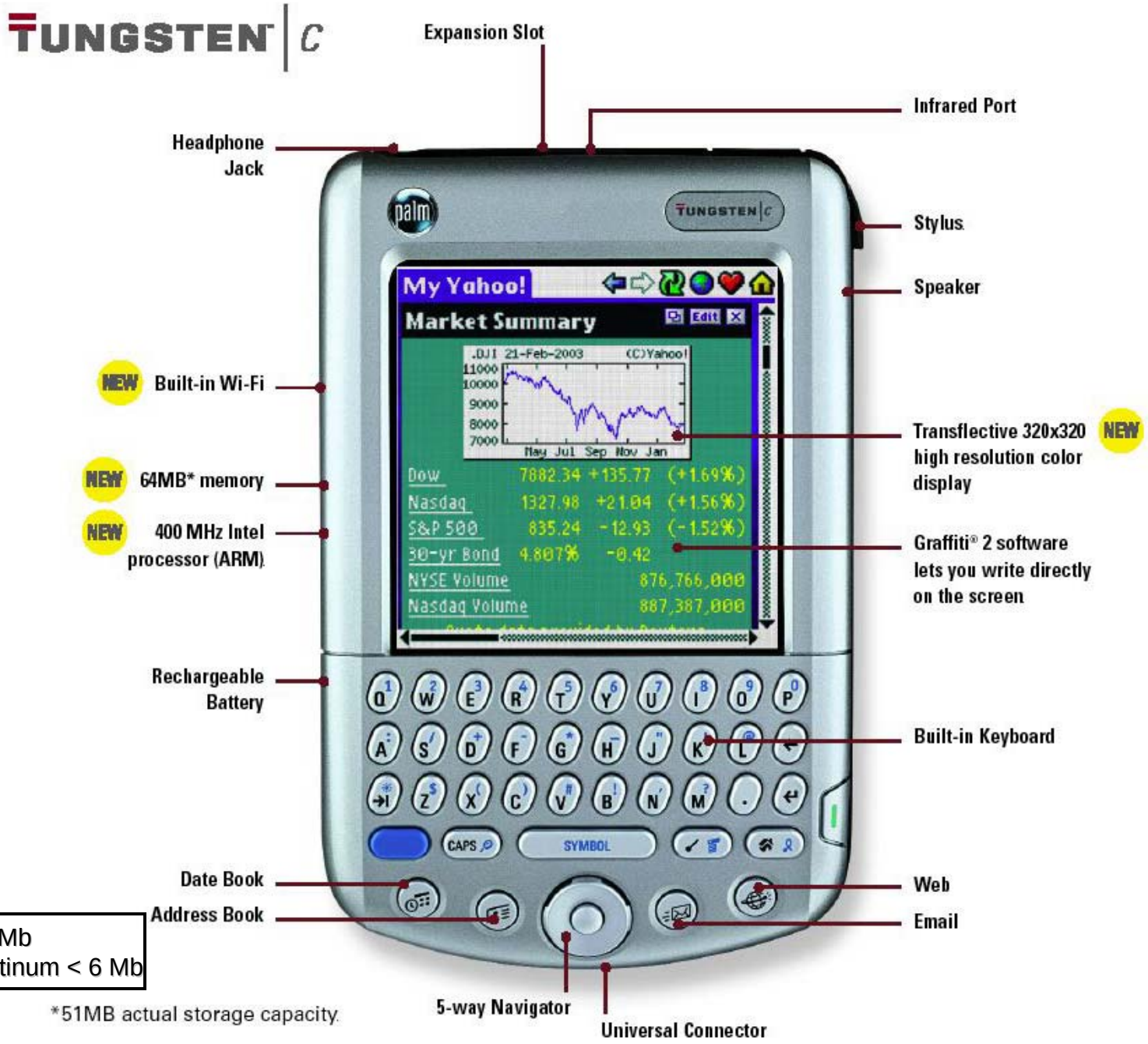
- Questions -

- How will this work?
- Is there a precedent for this type of approach to DILI causation?
- Will the instrument ultimately be user friendly?
- Will it be a lot of work to set up?
- Will it be worth the effort?

A Bayesian Approach

- Major Tasks -

- Establish a database of drug-specific PrOs based on:
  - RCT - published + unpublished
  - Standard texts
  - Expert opinion
- Establish a database of LRs
  - Some LRs may be stable - e.g., HBsAg, ANA, etc.
- Sensitivity analysis
- Compare with RUCAM, expert opinion
- Develop user-friendly computer interface



ePocrates < 2 Mb
Lexi-Drugs Platinum < 6 Mb

*51MB actual storage capacity.

A Bayesian Approach

- Other examples of computer-based Bayesian programs
  - MacBARDI-Q+A
  - BRCAPRO - Duke

A Bayesian Approach

- MacBARDI-Q+A : a prototype program
  - "Bayesian Adverse Diagnostic Instrument"
  - Excel spreadsheet on a Macintosh II
  - Neutropenia, GBS, pulmonary fibrosis, cutaneous reactions, etc…secondary to drugs
  - Cross-validated vs results from an *in vitro* assay (LTA) - 96% concordance

Lanctot and Naranjo

A Bayesian Approach

- Questions -

- Our instrument needs to take into account competing causes
  - How to do this? A negative test will increase posterior probability slightly, while a positive test may decrease it dramatically
  - Will LRs for standard lab tests be stable?
    - HBV Sag, HCV RNA, ANA, etc…
  - Are the LRs for such tests independent (or is there concordance)?

A Bayesian Approach

- What would use as a “gold standard” to compare with this novel instrument
  - In DILIN, we could assess causality using final adjudication from the Causality Committee.
- But, to make the 2 x 2 analysis worthwhile:
  - We need adequate number of cases.
  - We need “Possible” and “Unlikely” cases.

- Courtesy of J. Rochon

Hematologic dyscrasia associated with ticlopidine therapy: evidence for causality

Fran L. Paradiso-Hardy,* C. Mark Angelo,§ Krista L. Lanctôt,† Eric A. Cohen‡

- Used BARDI to assess risk of ticlopidine-induced blood dyscrasia
  - Obtained prior odds of from placebo controlled trials
  - Calculated LRs for hx, timing, characteristics, de- and re-challenge
  - Did sensitivity analysis over a range of PrO and LRs

CMAJ 2000; 163:1441-1448

Hematologic dyscrasia associated with ticlopidine therapy: evidence for causality

Fran L. Paradiso-Hardy,* C. Mark Angelo,§ Krista L. Lanctôt,† Eric A. Cohen‡

- Calculation of LRs: “conservative estimate based on clinical experience and consensus among us”
- LR =10 for dyscrasia secondary to enalapril because incidence of enalapril-induced dyscrasia increased from 0.02 to 0.2 in the setting of renal failure

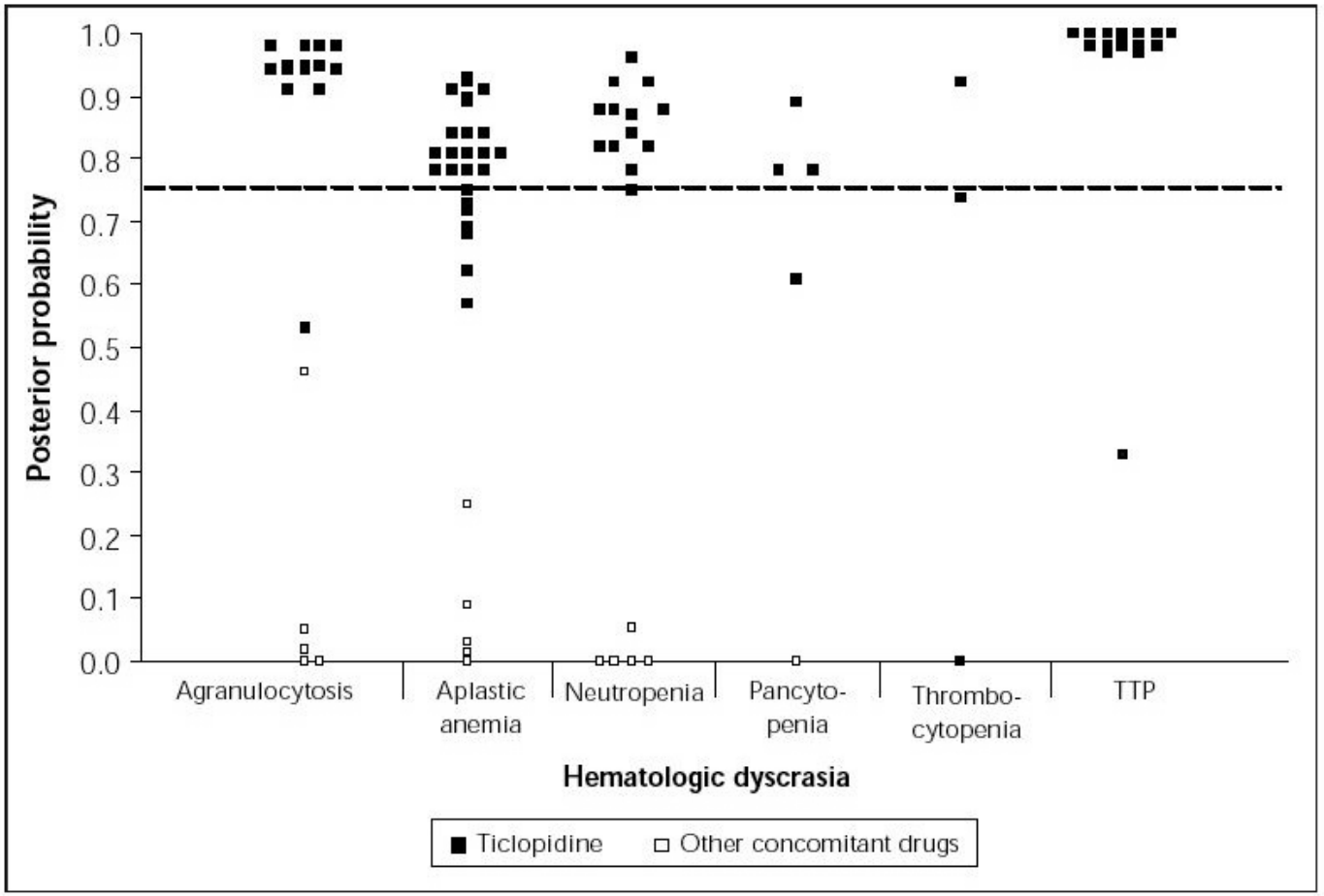


Fig. 1: Posterior probabilities for 91 case reports of hematologic dyscrasia associated with ticlopidine therapy. The posterior probability was 0.75 or greater (indicating a probability of at least 75% that ticlopidine caused the dyscrasia) (dashed line) in 82 (90%) of the case reports. TTP = thrombotic thrombocytopenic purpura.

Paradiso-Hardy et al

Table 3: Prior odds for the various types of hematologic dyscrasia

Drug	Agranulocytosis	Aplastic anemia	Neutropenia	Pancytopenia	Thrombocytopenia	TTP
Ticlopidine	4.4[78]	2.7[28]	2.2[78]	2.7[28]	1.0*	56.1[82,83]
ASA	–	2.9[76]	–	–	–	–
Allopurinol	–	–	0.536[79]	–	–	–
Digoxin	2.5[77,78]	–	–	–	–	–
Dipyridamole	3.8[77,78]	–	–	–	–	–
Enalapril	0.0161[81]	–	0.0536[80]	–	–	–
Furosemide	–	3.8[28,77]	–	–	–	–
HCTZ		0.5[28,77]		1.3[28,77]		

*Source: product monograph, Hoffmann–La Roche Limited, Mississauga, Ont.

Paradiso-Hardy et al

Table 4: Median prior and posterior probabilities for the various types of hematologic dyscrasia

Variable	Agranulocytosis	Aplastic anemia	Neutropenia	Pancytopenia	Thrombocytopenia	TTP
Median prior probability	0.81	0.73	0.69	0.73	0.50	0.98
Median posterior probability	0.95	0.81	0.86	0.78	0.74	1.00

Paradiso-Hardy et al

Hematologic dyscrasia associated with ticlopidine therapy: evidence for causality

Fran L. Paradiso-Hardy,* C. Mark Angelo,§ Krista L. Lanctôt,† Eric A. Cohen‡

- The authors admit that BARDI has limitations
  - Significant resources for an exhaustive literature search
  - Complex and tedious
    - Did not use spreadsheet

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- "The reason that we do not use this method routinely in clinical practice is probably because it takes too much time and effort to be specific, clear and coherent." - Hutchinson TA: CMAJ 2000; 163:1463-64.

What we have…

What we want…